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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/762,128	SCHOLLER ET AL.	
	Examiner	Art Unit	
	Anne-Marie Falk, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 April 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7 and 9-20* is/are pending in the application.

4a) Of the above claim(s) *11 and 14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7,9,10,12,13 and 15-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 January 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed August 31, 2007 (hereinafter referred to as "the response") has been entered. Claim 7 has been amended. Claims 1-6 and 8 have been cancelled and Claims 9-20 have been newly added.

The elected invention is drawn to a vaccine comprising one or more recombinant expression constructs (i.e., DNA vaccine compositions).

The response to the election of species requirement, filed November 16, 2007, has been entered. Applicants elected HER2 as the cell surface receptor antigen, along with a growth factor binding domain, CD86/B7.2, as the second immune response altering molecule, and a nucleic acid encoding IFN-gamma.

Claims 7 and 9-20 are pending in the instant application.

Claims 11 and 14 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on December 17, 2007.

Accordingly, Claims 7, 9, 10, 12, 13, and 15-20 are examined herein.

The rejection of Claims 1, 3, 5, and 7 under 35 U.S.C. 102(e), as being anticipated by U.S. Patent No. 6,348,450 (Tang et al., priority to 8/13/1997), is withdrawn in view of the amendments to Claim 7 and the cancellation of Claims 1, 3, and 5.

The rejection of Claims 1, 3, 5, and 7 under 35 U.S.C. 103(a), as being unpatentable over Conry et al. (1996, of record), is withdrawn in view of the amendments to Claim 7 and the cancellation of Claims 1, 3, and 5.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 7, 9, 10, 12, 13, and 15-20 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over Claims 1-4 of U.S. Patent No. 6,734,172. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the earlier-filed application are directed to a species that falls within the presently claimed genus. Thus, the claims of the patent anticipate the present claims (anticipation analysis).

At page 5 of the response, Applicants state that they will file a terminal disclaimer upon the allowance of claimed subject matter. Accordingly, the rejection is maintained until such time as a terminal disclaimer is filed.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Claims 7, 9, 10, 12, 13, and 15-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a vaccine composition for eliciting or increasing the titer of antibodies for Her2/neu protein, wherein the vaccine composition comprises one or more individual expression constructs encoding Her2/neu, CD86/B7.2, and 4-1BB ligand, and either CD86/B7.2 or CD80/B7.1, does not reasonably provide enablement for other vaccine compositions for eliciting or increasing the titer of antibodies for any cell surface receptor antigen, wherein the vaccine composition comprises one or more recombinant expression constructs encoding any cell surface receptor antigen plus any immune response altering molecule in combination with 4-1BB ligand, as set forth in the specification. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, are set forth in *In re Wands*, 8 USPQ2d 1400, at 1404 (CAFC 1988). These factors include: (1) the nature of the invention, (2) the state of the prior art, (3) the relative level of skill of those in the art, (4) the predictability of the art, (5) the breadth of the

claims, (6) the amount of direction or guidance presented, (7) the presence or absence of working examples, and (8) the quantity of experimentation necessary (MPEP 2164.01(a)).

Giving due consideration to all the Wands factors, with the most relevant factors discussed hereinbelow, it is concluded that the specification fails to provide an enabling disclosure for the full scope of the claims, for the reasons that follow.

Nature of the invention and scope of the claims. The claims are drawn to a composition for eliciting or increasing the titer of antibodies specific for a cell surface receptor antigen, comprising one or more recombinant expression constructs comprising at least one promoter operably linked to cassettes encoding a cell surface receptor antigen (SRA), a first immune response altering molecule (IRAM), and a second IRAM, wherein said first and second IRAMs are different from each other and are selected from the group consisting of an accessory cell agent and a T cell agent. Claim 7 is directed to a composition comprising at least two recombinant expression constructs encoding all three components. Claim 9 is directed to a composition comprising two recombinant expression constructs, one encoding the SRA and a second encoding a first IRAM and the second IRAM. Claim 10 is directed to a composition comprising three recombinant expression constructs, each encoding one component. The claims cover vaccines for cancer immunotherapy or any other purpose. The specification discloses an intended use for producing a protective or prophylactic immune response.

Amount of direction or guidance presented and the presence or absence of working examples. The specification describes the construction of four recombinant expression constructs based on the plasmid pLNCX. The four plasmids generated were designated pLNCX-4-1BBlig, pLNCX-B7.1, pLNCX-B7.2, and pLNCX-Rat-Neu and the CMV promoter was used to drive expression of each component. The plasmid pLNCX-4-1BBlig contains a gene encoding the murine 4-1BB ligand. pLNCX-B7.1 contains a cDNA sequence encoding murine B7.1. pLNCX-B7.2 contains a cDNA encoding murine B7.2. pLNCX-Rat-Neu contains a gene encoding the rat Neu surface receptor antigen.

FVB/N-TgN(MMTVneu) were used for immunization studies. The mice are transgenic for the rat Neu2 transgene under the control of a mouse mammary tumor virus promoter (MMTV LTR) and develop spontaneous mammary tumors with advanced age. Seven groups of mice were vaccinated with the plasmids by intradermal injection, as follows: pLNCX (Group 1, control), pLNCX-Rat-Neu (Group 2), pLNCX-Rat-Neu + pLNCX-B7.1 (Group 3), pLNCX-Rat-Neu + pLNCX-B7.2 (Group 4), pLNCX-Rat-Neu + pLNCX-4-1BBlig (Group 5), pLNCX-Rat-Neu + pLNCX-B7.1 + pLNCX-4-1BBlig (Group 6), pLNCX-Rat-Neu + pLNCX-B7.2 + pLNCX-4-1BBlig (Group 7). A booster immunization was injected 15 days later along with a dorsal subcutaneous challenge with mammary tumor cells from untreated transgenic mice. Neu-specific antibodies were detected in the sera of immunized mice by antigen-capture ELISA. Groups 3, 5, 6, and 7 all exhibited significantly elevated levels of anti-Neu antibodies compared to the control and Group 2 mice immunized with pLNCX-Rat-Neu alone. Tumor surface area increased as a function of time in mice of all treatment groups. An impaired tumor growth rate and decreased tumor burden were apparent in Group 7 mice. Group 4 mice, immunized with pLNCX-Rat-Neu + pLNCX-B7.2, exhibited an **increase** in tumor size and an increase in tumor growth rate.

The specification contemplates that the claimed vaccine may include expression constructs encoding a huge variety of immune response altering molecules (IRAM) (pages 11-16) in combination with any cell surface receptor antigen (pages 8-10). However, only the combinations discussed above are described. The specification fails to describe or provide specific guidance for any other combination that would elicit antibodies specific for a cell surface receptor antigen. While the specification contemplates a wide variety of agents that may be used as IRAM and a wide variety of agents that may be used as the SRA, the specification provides no guidance at all for specific combinations of two IRAM with one cell surface receptor antigen that would elicit an antibody response, other than the two combinations discussed above for producing Neu-specific antibodies, where a gene encoding either B7.1 or B7.2 is used in combination with genes encoding 4-1BB ligand and rat Neu. The specification provides **no** specific

guidance for other combinations. Thus, the specification fails to provide an enabling disclosure for other combinations that would elicit SRA-specific antibodies.

Beyond the specific vaccines exemplified, the specification provides only general guidance with regard to vector design and construction and possible promoters and other regulatory elements that could be used to drive expression of the three genes included in the vaccine. Specific guidance is not provided for achieving expression in appropriate cell types at levels suitable to elicit a protective antibody response.

State of the prior art and predictability of the art. The claims encompass DNA vaccines as well as viral vector vaccines which fall into the realm of gene therapy. However, gene therapy and DNA vaccination are not routinely successful. Therefore, the disclosure must enable the full scope of the claimed vaccine compositions with specific guidance.

At the outset it is noted that the term "vaccine" denotes an intended use for producing a protective or preventive immune response.

As a first issue, the specification fails to provide specific guidance on the parameters for vaccine delivery over the very broad scope of the claims. **Eck et al.** (1996, of record) teaches that numerous factors complicate the gene therapy art (page 81), which have not been shown to be overcome by routine experimentation. These include the following: the fate of the DNA vector itself (volume of distribution, rate of clearance into tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. These factors differ dramatically based on the vector used, the protein being produced, and the disease being treated.

As a second issue, the disclosure of a single embodiment of a well-known tumor cell surface receptor antigen (i.e., Her2/Neu) delivered as a recombinant expression vector in combination with two well-known immune response altering molecules (i.e., 4-1BB ligand and B7-2) into a mouse model prior to tumor formation is insufficient evidence of enablement for any vaccine delivering any cell surface receptor antigen by any route of delivery in combination with any two accessory molecules. No general guidelines existed at the time of filing or at present for the synthesis of recombinant expression constructs for the effective delivery of target antigens for vaccination. Undue experimentation would have been required for one skilled in the art to determine whether or not a selected vaccine composition could elicit or enhance antibody titers specific to any cell surface receptor antigen, particularly at a level that would be protective. Furthermore, undue experimentation would have been required for one skilled in the art to determine whether or not any combination of two IRAMs are co-stimulatory, and further determine which IRAMs work with which cell surface receptor antigen. Thus, the specification fails to enable the full scope of the claimed vaccine.

As a third issue, Applicants' own examples demonstrate the unpredictability in the art of DNA vaccines. The specification provides evidence that one group of mice (Group 4), immunized with component vaccine DNA constructs pLNCX-Rat-Neu + pLNCX-B7.2, did **not** exhibit an increased antibody titer compared to controls and did **not** provide any degree of protection upon disease challenge. In fact, the Group 4 mice exhibited an **increased** tumor growth rate and tumors of increased size as compared to controls (Figure 3). Furthermore, Group 5 mice, immunized with pLNCX-Rat-Neu + pLNCX-4-1BBlig, although exhibiting a slightly increased antibody response as compared to controls, did not exhibit any anti-tumor response, thereby demonstrating that an increased antibody response does not correlate to an anti-tumor response. Therefore, these combinations of DNA vaccine constructs did not function as a vaccine and aptly demonstrates the unpredictability in the art of DNA vaccines which cannot be overcome by routine experimentation.

As a fourth issue, cancer immunotherapy is not routinely successful and the DNA vaccine art is highly unpredictable. Thus, the art of developing DNA vaccines for cancer immunotherapy is also highly unpredictable. For example, with regard to DNA vaccines, **Leitner et al.** (2000, Vaccine 18:765-777) teaches that the expression level of the antigen, immunogenicity of the antigen, the strain of mouse being used to test the DNA vaccine and the age of the animals, all contribute to the unpredictable nature of DNA vaccines and the unpredictability inherent to different methods of assessing the efficacy of said DNA vaccines (see Table 1, page 767). Leitner et al. further note that "the efficacy of genetic vaccines in many systems has not proven to be satisfactory" (page 766, column 2) and that "[a]lthough genetic vaccines have been significantly improved, they may not be sufficiently immunogenic for the therapeutic vaccination of patients with infectious diseases or cancer in clinical trials" (abstract). The authors further note that antigens can be modified to make them better immunogens (page 769). While modified antigens fall within the scope of the claimed invention, the specification does not provide specific guidance for improving the immunogenicity of the SRA, using nothing more than routine experimentation. Although Leitner et al. acknowledge that intramuscular and intradermal DNA vaccination may employ different mechanisms in inducing immune responses, the instant specification provides no specific guidance on which vaccine compositions may be suitable for any given route of administration or which routes of administration would be appropriate for any given vaccine composition. Thus, in addition to testing a huge variety of possible combinations, the skilled artisan would need to test different routes of administration for each combination vaccine, different promoters, different mouse strains at varying ages or primate models, and possibly different modified forms of the antigen. Furthermore, since an antibody response does not necessarily correlate to an anti-tumor response or protective immune response, further experiments would be required to evaluate any possible anti-tumor effect or protective effect of the selected vaccine. As a result of the large number of parameters that affect the success of genetic vaccination, intensive investigation has met with limited success.

The state of the art is such that numerous problems exist in regards to administering a DNA vaccine to humans and large animals. **Babiuk et al.** (2003, Vaccine 21: 649-658) teaches that "[i]t is generally recognized that DNA vaccines are often less effective in large animals than in mice" (abstract). With regard to the use of co-stimulatory strategies in combination with DNA vaccines, the authors note that "[t]he complexity of the biological actions of co-stimulatory molecules and cytokines will require much more testing to design optimal stimulation for DNA vaccines" (page 652, column 2, paragraph 3).

The specification fails to provide specific guidance on routes of administration for the various combination vaccines covered by the broad scope of the claims, particularly with regard to raising a protective antigen-specific antibody response. The specification only teaches the use of intradermal injection for raising an anti-tumor antibody response (page 53, lines 20-21), and beyond that, the specification provides only general guidance with regard to routes of administration that were known in the art for DNA vaccines in general. **McCluskie et al.** (1999, Mol. Med. 5:287-300) teaches that the route of delivery of a DNA vaccine influences immune responses in laboratory animals (abstract) Specifically, in one study McCluskie et al. only observed antibody responses to injected routes of administration of DNA vaccines and not to non-injected routes of administration of DNA vaccines, such as oral routes, sublingual, inhalation, and vaginal wall, because of variation in transfection efficiency (abstract). Among the injected routes, only 5 of 8 routes produced an antibody response. Furthermore, McCluskie et al. teaches that the strength and nature of immune responses to administration of DNA vaccines varies between species and that it is not clear that results from one species are predictive in another (abstract).

The specification fails to provide specific guidance on the multitude of parameters that affect the effectiveness of DNA vaccines. Given the very large number of possible combinations of the three vaccine components, considered with the different types of vectors, promoters, and other regulatory elements that may be used to control expression of the components, considerable guidance is needed to

identify a set of parameters that will produce a protective antigen-specific antibody response. **Finn** (2003, Nature Reviews Immunology 3:630-641) teaches numerous factors that determine the effectiveness of a vaccine, such as choosing the right antigen, choosing the right adjuvant, generating the right type of immune response, and elicitation of long-term memory (pages 630-633). Finn further points out that tumor-induced immunosuppression and immune evasion are additional issues that confound the effectiveness of cancer vaccines (page 634). Thus, given the large number of parameters that may be varied, with no guidelines that are generally applicable to the disparate diseases that may be targeted for treatment, considerable experimentation is required to identify vaccines within the scope of the claims that are capable of producing a protective antibody response.

Another factor affecting the immunogenicity of any DNA vaccine is the nucleotide sequence itself. **Donnelly et al.** (1997, Annual Review of Immunology 15:617-648, of record) teaches that "[c]ertain CpG motifs can be stimulatory or inhibitory, suggesting that the presence or absence of these sequences in DNA vaccines could affect the immunogenicity of the vaccine" (page 638, paragraph 1) and that "[t]hese observations suggest that the plasmid itself functions as an adjuvant or immunomodulator" (page 638, pargraph 1). The authors go on explicitly point out that "[a]ltering the nucleotide sequence of the vector may affect the immunogenicity of DNA vaccines" (page 638, paragraph 1). However, since some motifs are stimulatory and some inhibitory, the effect will be unpredictable. Thus, there are no clear guidelines for developing DNA vaccines that produce the desired response.

Absent specific guidance for identifying other vaccine compositions that produce the claim-designated response, the skilled artisan would have been required to engage in trial and error experimentation. Such experimentation clearly would rise to the standard of undue experimentation.

The art clearly demonstrates that DNA vaccines produce unpredictable responses and that considerable experimentation is required to produce a desired response. Thus, the prior art shows that intensive investigation has met with limited success.

The specification provides no guidance beyond the single working example on how to select an appropriate combination of elements for eliciting a protective antibody response. Since one of skill in the art would not know **what** to make, the skilled artisan would not know **how** to make vaccine compositions that elicit a protective antibody response. Furthermore, for any given combination of elements, given the high degree of unpredictability inherent to the art of DNA vaccination, one of skill in the art would not know how to use the vaccine composition in a manner suitable to raise a protective antibody response, because not all combinations will lead to a protective antibody response. Given the likelihood for a high number of inoperable embodiments that fall within the scope of the claim, one of skill in the art would not know how to distinguish the operable embodiments from the inoperable embodiments, using only routine experimentation.

The court has recognized that physiological activity is unpredictable. *In re Fisher*, 166 USPQ 18 (CCPA 1970). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved. *In re Fisher*, 166 USPQ 18 (CCPA 1970).

It is not to be left up to the skilled artisan to figure out how to make the necessary starting materials and then to figure out how to use them to produce the biological effects as recited in the claims. The courts held that the disclosure of an application shall inform those skilled in the art how to use applicant's claimed invention, not how to **find out** how to use it for themselves. *In re Gardner et al.* 166 USPQ 138 (CCPA 1970). This specification only teaches what is intended to be done and how it is intended to work, but does not actually teach how to do that which is intended.

Given the unpredictability in the art of DNA vaccination, gene therapy, and cancer immunotherapy, the limited working examples directed to a single combination of antigen plus a first and second IRAM, the limited guidance in the specification for identifying other combinations that would produce the claimed effect, and the broad scope of the claims, undue experimentation would have been

required to make and use the claimed vaccine compositions to produce a protective antibody response over the full scope, which covers a vast array of combinations of the three agents specified in the claims in conjunction with additional elements not specified in the claims.

At pages 6-7 of the response, Applicants assert that the Examiner has not established a *prima facie* case on non-enablement for the claimed invention. Applicants allege that the specification enables the full scope of the claims as amended. However, ample reasons for lack of enablement have been provided and the appropriate *Wands* analysis has been performed. The instantly claimed invention is directed to expression constructs that encode three different agents, each of which must be delivered to the appropriate site and expressed at a level appropriate to elicit the desired effect, i.e. eliciting antibodies specific for the cell surface receptor antigen encoded by the expression construct. The claimed composition is comprised of one or more expression constructs. Thus, gene delivery with subsequent gene expression at a level and location appropriate to elicit the desired response is a critical aspect of the invention. Furthermore, as the design and development of this type of composition is inherently unpredictable, one skilled in the art would not be able to produce similar compositions for other SRAs, using other immune response altering molecules (IRAMs), without undue experimentation. While the specification presents a vast array of IRAMs that may be used in the present invention, the specification only provides a starting point (i.e., the scope of enablement indicated above) for identifying other embodiments of the claimed invention that will elicit the claimed response, but the specification does not provide guidance on the direction in which experimentation should proceed. Absent specific guidance for identifying other compositions that produce the claimed response, the skilled artisan would have been required to engage in trial and error experimentation. Such experimentation clearly would rise to the standard of undue experimentation.

At page 8 of the response, Applicants point out that transgenic mice expressing the rat Neu2 transgene were injected with plasmids encoding rat Neu, 4-1BB ligand, and either B7.1 or B7.2.

Applicants point out that combinations including either B7.1 or B7.2 were effective for increasing the titer of antibodies for the cell surface receptor antigen. Applicants further point to the results depicted in Figure 1 for the Group 6 and Group 7 mice. Accordingly, the scope of enablement set forth above has been revised to include constructs encoding either B7.1 or B7.2.

At page 9 of the response, Applicants cite a 2003 reference of Disis et al. for describing a plasmid encoding rat Neu and a single plasmid encoding two co-stimulatory molecules, either CD137L/IRES/CD80 or CD137L/IRES/CD86, used to vaccinate mice. Applicants point out that the CD137 ligand corresponds to 4-1BB-ligand. Applicants further note that a significant antibody response was detected in mice vaccinated with pLNCX-rat Neu and either CD137L/CD80 or CD137L/CD86. However, given that the effective filing date of the instant application is 1998, the reference is post-filing art, and therefore one of skill in the art would not have had the benefit of the teachings of the Disis et al. reference at the time of filing.

At pages 9-10 of the response, Applicants assert that the Disis et al. reference showed that transcripts of the introduced gene could be detected in the lymph nodes of the immunized mice even at the lowest dose of plasmid. However, such a finding does not obviate the unpredictability in the art, as some protocols may be successful while others will not. The issue is that it is unpredictable which protocols will work and which will not. As such, trial and error experimentation is needed to determine which protocols work and which do not. Absent specific guidance regarding which combinations of IRAMs to use with a particular cell surface receptor antigen, to which one hopes to provoke a humoral response, the skilled artisan would have been left to experiment by trial and error, with no clear guidelines on the direction in which experimentation should proceed. The courts have stated that "a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing *In re*

Angstadt, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976)). However, in the instant case, there is no teaching of the direction in which experimentation should proceed and trial and error experimentation does not constitute routine experimentation.

At page 11 of the response, Applicants assert that the specification provides adequate guidance with regard to methods of administration of the composition, such as dosages and various routes of administration. However, the guidance offered in the specification at pages 45-46 is in the form of general guidance rather than specific guidance. General guidance is not sufficient in unpredictable areas where specific guidance is needed to enable the invention.

The unpredictability of a particular art area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See *Ex parte Singh*, 17 USPQ2d 1714 (BPAI 1991). It is also well established in case law that the specification must teach those of skill in the art how to make and how to use the invention as broadly claimed. *In re Goodman,* 29 USPQ2d at 2013 (Fed. Cir. 1994), citing *In re Vaeck*, 20 USPQ2d at 1445 (Fed. Cir. 1991).

While the PTO bears the initial burden of providing reasons for doubting the objective truth of the statements made by Applicants as to the scope of enablement, when the PTO meets this burden, the burden shifts to applicant to provide suitable evidence indicating that the specification is enabling in a manner commensurate in scope with the protection sought by the claims. *In re Marzocchi*, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 7, 9, 10, 12, 13, and 15-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 7, 9, 10, 12, 13, and 15-20 are indefinite in their recitation of "increasing" because it is unclear relative to what standard or point of reference the antibody titer is considered to be "increased." The term "increasing" is a relative term which renders the claim indefinite. The term "increasing" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Thus, the metes and bounds are not clearly set forth.

At page 5 of the response, Applicants state that they have replaced the term "enhancing" with the term "increasing." However, the term "increasing" has the same problem as the term "enhancing."

Conclusion

No claims are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

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questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (571) 272-0728. The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on (571) 272-4517. The central official fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Anne-Marie Falk, Ph.D.

/Anne-Marie Falk/
Primary Examiner, Art Unit 1632